Xenon as an adjuvant to therapeutic hypothermia in near-term and term newborns with hypoxic-ischaemic encephalopathy

Rüegger, Christoph M ; Davis, Peter G ; Cheong, Jeanie L

Abstract: BACKGROUND Hypoxic-ischaemic encephalopathy (HIE) is a serious birth complication affecting term and late preterm newborns. Although therapeutic hypothermia (cooling) has been shown to be an effective therapy for neonatal HIE, many cooled infants have poor long-term neurodevelopmental outcomes. In animal models of neonatal encephalopathy, inhaled xenon combined with cooling has been shown to offer better neuroprotection than cooling alone. OBJECTIVES To determine the effects of xenon as an adjuvant to therapeutic hypothermia on mortality and neurodevelopmental morbidity, and to ascertain clinically important side effects of xenon plus therapeutic hypothermia in newborn infants with HIE. To assess early predictors of adverse outcomes and potential side effects of xenon. SEARCH METHODS We used the standard strategy of the Cochrane Neonatal Review Group to search the Cochrane Library (2017, Issue 8), MEDLINE (from 1966), Embase (from 1966), and PubMed (from 1966) for randomised controlled and quasi-randomised trials. We also searched conference proceedings and the reference lists of cited articles. We conducted our most recent search in August 2017. SELECTION CRITERIA We included all trials allocating term or late preterm encephalopathic newborns to cooling plus xenon or cooling alone, irrespective of timing (starting age and duration) and concentrations used for xenon administration. DATA COLLECTION AND ANALYSIS Two review authors independently assessed results of searches against predetermined criteria for inclusion, assessed risk of bias, and extracted data. We performed meta-analyses using risk ratios (RRs), risk differences (RDs), and number needed to treat for an additional beneficial outcome (NNTB) with 95% confidence intervals (CIs) for dichotomous outcomes and mean differences (MDs) for continuous data. MAIN RESULTS A single randomised controlled trial enrolling 92 participants was eligible for this review. Researchers have not reported long-term neurodevelopmental outcomes, including the primary outcome of this review - death or long-term major neurodevelopmental disability in infancy (18 months to three years of age). Cooling plus xenon was not associated with reduced mortality at latest follow-up, based upon low quality evidence. Investigators noted no substantial differences between groups for other secondary outcomes of this review, such as biomarkers of brain damage assessed with magnetic resonance imaging and occurrence of seizures during primary hospitalisation. Available data do not show an increased adverse event rate in the cooling plus xenon group compared with the cooling alone group. AUTHORS' CONCLUSIONS Current evidence from one small randomised controlled pilot trial is inadequate to show whether cooling plus xenon is safe or effective in near-term and term newborns with HIE. Further trials reporting long-term neurodevelopmental outcomes are needed.

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[Intervention Review]

Xenon as an adjuvant to therapeutic hypothermia in near-term and term newborns with hypoxic-ischaemic encephalopathy

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ABSTRACT

Background

Hypoxic-ischaemic encephalopathy (HIE) is a serious birth complication affecting term and late preterm newborns. Although therapeutic hypothermia (cooling) has been shown to be an effective therapy for neonatal HIE, many cooled infants have poor long-term neurodevelopmental outcomes. In animal models of neonatal encephalopathy, inhaled xenon combined with cooling has been shown to offer better neuroprotection than cooling alone.

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To determine the effects of xenon as an adjuvant to therapeutic hypothermia on mortality and neurodevelopmental morbidity, and to ascertain clinically important side effects of xenon plus therapeutic hypothermia in newborn infants with HIE. To assess early predictors of adverse outcomes and potential side effects of xenon.

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We used the standard strategy of the Cochrane Neonatal Review Group to search the Cochrane Library (2017, Issue 8), MEDLINE (from 1966), Embase (from 1966), and PubMed (from 1966) for randomised controlled and quasi-randomised trials. We also searched conference proceedings and the reference lists of cited articles. We conducted our most recent search in August 2017.

Selection criteria

We included all trials allocating term or late preterm encephalopathic newborns to cooling plus xenon or cooling alone, irrespective of timing (starting age and duration) and concentrations used for xenon administration.

Data collection and analysis

Two review authors independently assessed results of searches against predetermined criteria for inclusion, assessed risk of bias, and extracted data. We performed meta-analyses using risk ratios (RRs), risk differences (RDs), and number needed to treat for an additional beneficial outcome (NNTB) with 95% confidence intervals (CIs) for dichotomous outcomes and mean differences (MDs) for continuous data.

Main results

A single randomised controlled trial enrolling 92 participants was eligible for this review. Researchers have not reported long-term neurodevelopmental outcomes, including the primary outcome of this review - death or long-term major neurodevelopmental disability in infancy (18 months to three years of age). Cooling plus xenon was not associated with reduced mortality at latest follow-up, based upon low quality evidence. Investigators noted no substantial differences between groups for other secondary outcomes of this review, such as biomarkers of brain damage assessed with magnetic resonance imaging and occurrence of seizures during primary hospitalisation. Available data do not show an increased adverse event rate in the cooling plus xenon group compared with the cooling alone group.

Authors' conclusions

Current evidence from one small randomised controlled pilot trial is inadequate to show whether cooling plus xenon is safe or effective in near-term and term newborns with HIE. Further trials reporting long-term neurodevelopmental outcomes are needed.

PLAIN LANGUAGE SUMMARY

Cooling plus inhaled xenon for newborns with hypoxic-ischaemic encephalopathy

Review question: How does cooling plus inhaled xenon compare with cooling alone for improving survival and development of newborn babies who may have suffered from lack of oxygen at birth?

Background: Hypoxic-ischaemic encephalopathy, or HIE, is a brain injury caused by oxygen deprivation to the brain during birth (birth asphyxia). Hypoxic-ischaemic encephalopathy is a leading cause of death or severe impairment among infants. Therapeutic hypothermia (cooling) is a treatment option available to reduce the chances of severe brain damage when an infant's body temperature is reduced shortly after birth. Although cooling has been shown to be an effective therapy for neonatal HIE, half of treated newborn babies still die or face neurodevelopmental sequelae later in life. Evidence indicates that inhaled xenon, an odourless gas, in combination with body cooling, can help to improve survival and development at 18 to 36 months.

Study characteristics: This review found a single randomised controlled trial that examined the short-term effects of cooling plus xenon for infants with HIE.

Key results: This trial enrolled 92 participants. Cooling plus xenon did not improve clinical outcomes before discharge from the hospital compared with cooling alone. Data on long-term development were not provided.

Quality of evidence: Current low quality evidence is inadequate to show whether cooling plus xenon improves survival and development of newborn babies with HIE. Evidence is up-to-date as of August 2017.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Cooling plus xenon compared with cooling alone for newborns with hypoxic-ischaemic encephalopathy

Patient or population: late preterm or term newborns with hypoxic-ischaemic encephalopathy
Settings: neonatal intensive care unit
Intervention: cooling plus xenon
Comparison: cooling alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with cooling alone	Risk with cooling plus xenon				
Death or major neurodevelopmental disability in infancy	No data	No data	No data	No data	Absence of evidence	
Mortality at latest reported age	Study population		RR 1.22 (0.56 to 2.67)	92 (1 RCT)	⊕⊕◯◯ **Low**	Single study Unblinded trial
	196 per 1000	239 per 1000				
Major neurodevelopmental disability in infancy	No data	No data	No data	No data	Absence of evidence	
Major neurodevelopmental disability at school age	No data	No data	No data	No data	Absence of evidence	
Cerebral palsy in infancy	No data	No data	No data	No data	Absence of evidence	
Developmental delay or intellectual impairment in infancy	No data	No data	No data	No data	Absence of evidence	

Blindness vision in infancy	No data	No data	No data	No data	Absence of evidence
Sensorineural deafness in infancy requiring amplification	No data	No data	No data	No data	Absence of evidence

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; RCT: randomised controlled trial; RR: risk ratio

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

BACKGROUND

Description of the condition

Intrapartum asphyxia is the third leading cause of child death globally (Liu 2015). It is estimated that each year, over 0.7 million affected newborns die and 1.15 million develop acute disordered brain function known as 'hypoxic-ischaemic encephalopathy (HIE)' (Lee 2013). HIE, which is one of the most common causes of childhood neurodisability worldwide, results in considerable psychosocial and economic impact for families and society (Lawn 2014). Induced therapeutic hypothermia (body cooling) has emerged as an effective neuroprotective strategy for term and late preterm newborns with moderate to severe HIE. However, in the developed world, half of treated infants still die or face neurodevelopmental sequelae later in life (Jacobs 2013).

Human and animal studies have demonstrated that the basic cascade of brain injury related to hypoxic-ischaemic insults typically occurs in distinct phases (Hassell 2015); in the acute phase, the culmination of energy failure, acidosis, glutamate release, lipid peroxidation, and the toxic effect of nitric oxide leads to cell death via necrosis and activates apoptotic cascades (Ferriero 2004). After partial recovery and a latent phase that lasts up to six hours, secondary deterioration occurs. This secondary phase is characterised by cytotoxic oedema, excitotoxicity, and secondary energy failure with nearly complete loss of mitochondrial activity (Douglas-Escobar 2015). In newborns with moderate to severe HIE, this secondary phase of injury is typically associated with clinical deterioration and increased seizure activity. Magnetic resonance spectroscopy (MRS), which is the most accurate quantitative magnetic resonance biomarker in the neonatal period for prediction of neurodevelopmental outcome after HIE (Thayyil 2010), shows that this secondary phase is generally accompanied by a second lactate elevation (Barkovich 1995). A tertiary phase involves active pathological processes that occur for months after a hypoxic-ischaemic insult, including late cell death, remodelling of the injured brain, and astrogliosis due to persistent inflammation and epigenetic changes (Fleiss 2012). It is the time period following resuscitation, before the secondary phase of injury, that provides a potential window for neuroprotection or diminution of injury.

Description of the intervention

Xenon is an odourless, dense, noble gas that has been approved as an inhalational anaesthetic in adults. Xenon has a rapid onset of action via inhalation and is eliminated unchanged via the lungs within minutes of cessation of delivery. Upon administration, xenon rapidly decreases amplitude-integrated electroencephalographic (aEEG) background activity (Sabir 2016), which is consistent with clinical findings that demonstrate its anticonvulsant and electroencephalographic (EEG) suppressant effects in infants with HIE (Azzopardi 2013). Small and large preclinical studies have evaluated its potential as a neuroprotective agent, when inhaled at a subanaesthetic concentration of 50% (Dingley 2006; Ma 2005). In animal models of moderate HIE, xenon significantly reduced brain injury and had an additive neuroprotective effect when combined with cooling immediately after the insult (Chakkarapani 2010; Dingley 2008; Liu 2015; Thoresen 2009). This benefit was sustained with complete restoration of long-term functional outcomes and improved regional histopathology (Hobbs 2008).

The optimal timing, dose, and duration of xenon inhalation have not yet been established. Xenon has been shown to be neuroprotective in neonatal rats when administered before (Ma 2006), during (Ma 2005), and after a hypoxic insult (Dingley 2006). When administered immediately or within hours after a hypoxic-ischaemic event, xenon had a significant effect at concentrations of 40% ($Xe_{40\%}$) and greater (Ma 2005). When combined with therapeutic hypothermia in a hypoxic-ischaemic pig model, xenon was effective and safe in concentrations up to 70% and for as long as 24 hours (Chakkarapani 2010; Dingley 2008; Faulkner 2011). Although $Xe_{70\%}$ has been suggested to be more neuroprotective than $Xe_{50\%}$, most preclinical studies used concentrations $\leq$ 50% that induced sedation and allowed administration of substantial concentrations of oxygen but did not result in respiratory depression (Dingley 2008).

In the field of adult critical care medicine, the cardiovascular, analgesic, and safety profile of xenon has been thoroughly evaluated (Dingley 2001; Rossaint 2003; Sanders 2005). In the paediatric population, however, its safety has not yet been assessed systematically. In a piglet model of HIE that closely resembles perinatal asphyxia, xenon together with therapeutic hypothermia improved cardiovascular stability and reduced the requirement for inotropes (Chakkarapani 2012). Investigators noted no increase in oxygen requirements, no cuffed tracheal tube complications, and no stridor or extubation delays either during or after xenon delivery (Chakkarapani 2010). Despite their favourable short-term safety profile, considerable controversy surrounds the lasting effects of anaesthetic agents on the developing brain in general (Sun 2010). Animal studies have demonstrated that general anaesthetic agents produce accelerated apoptosis and cause adverse effects on cognition and behaviour (Andropoulos 2017; Jevtovic-Todorovic 2013). Xenon acts mainly by inhibiting the N-methyl-D-aspartate (NMDA) receptor, but in contrast to other inhalation anaesthetic agents, xenon lacks dopamine-releasing properties and is not associated with an increase in neuroapoptosis (Faulkner 2011; Sabir 2013).

A major disadvantage of xenon is that it is difficult to use in clinical practice owing to its scarcity (0.0087 ppm in air) and high costs, along with the need for closed-circuit delivery (including cuffed tubes) and recycling systems.

How the intervention might work

Xenon is an NMDA receptor antagonist that prevents postsynaptic binding of the excitatory neurotransmitter glutamate (Franks 1998). It competitively binds to the glycine site of the receptor by interacting with the aromatic ring of phenylalanine (Armstrong 2012; Dickinson 2007). Researchers have demonstrated the neuroprotective properties of xenon in cell culture (Petzelt 2003), in a rodent model of hypoxia-ischaemia (Dingley 2008; Hobbs 2008; Ma 2005; Thoresen 2009; Zhuang 2012), and in a neonatal pig model of global hypoxia-ischaemia (Chakkarapani 2010; Faulkner 2011). Apart from its blocking effect on NMDA receptors, additional neuroprotective mechanisms have been identified. Xenon activates two species of potassium channels including the inwardly rectifying K_{ATP} channel, as reported in Bantel 2010, and the two pore domain K^+channels studied by Gruss 2004, both of which have been linked to neuroprotection. Other actions include inhibition of the calcium/calmodulin-dependent protein kinase II (Petzelt 2001), as well as activation of the antiapoptotic effectors Bcl-XL and Bcl-2 (Ma 2007). Furthermore, xenon increases the production of hypoxia-inducible factor 1 alpha (HIF-1 alpha) and its downstream effectors erythropoietin, vascular endothelial growth factor, and glucose transporter 1 protein, which can interrupt the apoptotic pathway (Ma 2009).

Through inhibition of NMDA receptors and reduction of apoptotic cell death, xenon is believed to exert most of its neuroprotective properties in the early and late phases of reperfusion injury.

Why it is important to do this review

Cooling has been shown to be an effective therapy for neonatal HIE. However, the rate of death and disability remains at about 50% in treated infants, necessitating the development of additional neuroprotective therapies. This is the first systematic review conducted to assess the evidence for xenon as an adjuvant to therapeutic hypothermia for newborns with HIE.

OBJECTIVES

To determine the effects of xenon as an adjuvant to therapeutic hypothermia on mortality and neurodevelopmental morbidity, and to ascertain clinically important side effects of xenon plus therapeutic hypothermia in newborn infants with HIE. To assess early predictors of adverse outcomes and potential side effects of xenon.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised controlled trials (RCTs) and quasi-RCTs that compare cooling plus xenon versus cooling alone.

Types of participants

1. Newborn infants at 35 weeks' gestation or greater with:
   i) evidence of peripartum asphyxia, with each enrolled infant satisfying at least one of the following criteria.
      a) Apgar score $\leq$ 5 at 10 minutes.
      b) Mechanical ventilation or resuscitation at 10 minutes.
      c) Cord pH < 7.1, or arterial pH < 7.1, or base deficit $\geq$ 12 within 60 minutes of birth.
   ii) evidence of encephalopathy according to Sarnat staging (Finer 1981; Sarnat 1976).
      a) Stage 1 (mild): hyperalertness, hyperreflexia, dilated pupils, tachycardia, absence of seizures.
      b) Stage 2 (moderate): lethargy, hyperreflexia, miosis, bradycardia, seizures, hypotonia with weak suck, and Moro.
      c) Stage 3 (severe): stupor, flaccidity, small to mid-position pupils that react poorly to light, decreased stretch reflexes, hypothermia, and absent Moro.
   iii) induced therapeutic hypothermia treatment (whole body or selective head cooling to 32°C to 34°C) initiated within six hours after birth; and
   iv) no major congenital abnormalities recognisable at birth.

Types of interventions

Inhaled xenon (irrespective of timing and concentrations used) as an adjuvant to therapeutic hypothermia versus therapeutic hypothermia alone, based on the following prespecified definitions.

1. Therapeutic hypothermia.
   i) Standard therapeutic hypothermia (whole body or selective head cooling to 32°C to 34°C initiated within six hours after birth and continued for 72 hours before slow rewarming.
2. Xenon administration.
   i) Irrespective of timing (starting age and duration) and concentrations used.

Types of outcome measures

Primary outcomes

The primary outcome measure was death or long-term major neurodevelopmental disability in infancy (18 months to three years of age) defined as the following.

1. Cerebral palsy (CP), graded according to the Gross Motor Function Classification System of Palisano 1997 for children two years of age and younger.

2. Developmental delay (Bayley or Griffith assessment more than two standard deviations (SD) below the mean).
3. Intellectual impairment (intelligence quotient (IQ) more than two SD below the mean).
4. Blindness (vision < 6/60 in both eyes).
5. Sensorineural deafness requiring amplification.

Secondary outcomes

Secondary outcomes included the following.

1. Mortality (all-cause mortality at latest reported age).
2. Major neurodevelopmental disability:
   i) in infancy (18 months to three years of age); and
   ii) at school age (> five years).
3. Major neurodevelopmental disability in infancy (18 months to three years of age) consists of the following components.
   i) CP, graded according to the Gross Motor Function Classification System of Palisano 1997 for children two years of age and younger.
   ii) Developmental delay or intellectual impairment.
      a) Bayley or Griffith assessment more than two SD below the mean or intellectual impairment (IQ more than two SD below mean).
      b) Neuromotor development (Bayley Scales of Infant Development - Psychomotor Development Index (BSID PDI)) assessed in survivors.
      c) Mental development (Bayley Scales of Infant Development - Mental Development Index (BSID MDI)) assessed in survivors.
   iii) Blindness (vision < 6/60 in both eyes).
   iv) Sensorineural deafness requiring amplification.
4. Cognitive and educational outcomes in survivors over five years of age.
   i) IQ and/or indices of educational achievement measured by a validated assessment tool including school examination results.
5. Additional predictors of neurodevelopmental outcome.
   i) Severity of encephalopathy at enrolment (Sarnat staging) (Finer 1981; Sarnat 1976).
   ii) Severity of EEG abnormality at enrolment.
      a) Severe: isoelectric or burst-suppression pattern.
      b) Moderate: low voltage or discontinuous background.
      c) Mild: electrographic seizures, dysmaturity.
   iii) Seizures.
      a) Seizures during initial hospitalisation.
      b) Seizures or need for anticonvulsants at follow-up.
   iv) Magnetic resonance imaging (MRI) abnormalities during primary hospitalisation.
      a) Moderate or severe abnormalities in the basal ganglia or thalamus, severe white matter lesions, or abnormalities in the posterior limb of the internal capsule (Rutherford 2010).
6. Potential adverse effects of xenon therapy during or immediately after administration.
   i) Heart rate.
      a) Sinus bradycardia (heart rate < 80 beats/min).
      b) Sinus tachycardia (heart rate > 180/min).
      c) Prolonged QT interval.
      d) Major arrhythmia (requiring medical intervention or cessation of xenon therapy, or both).
   ii) Blood pressure.
      a) Hypotension (mean arterial pressure (MAP) < 40 mmHg).
      b) Need for inotrope support.
   iii) Respiratory impairment.
      a) Pneumonia.
      b) Pulmonary air leak.
      c) Pulmonary haemorrhage.
      d) Persistent pulmonary hypertension (PPHN) (diagnosed clinically or by echocardiogram).
   iv) Cuffed endotracheal tube complications.
      a) Extubation stridor.
   v) Skin rashes.

Search methods for identification of studies

We conducted systematic searches for randomised controlled trials (RCTs) or quasi-RCTs and considered only parallel-group trials. We applied no language, publication year, or publication status restrictions.

Electronic searches

We used the criteria and standard methods of Cochrane and the Cochrane Neonatal Review Group. We undertook a comprehensive search of the following electronic sources.

We used MeSH terms and keywords to search the following.

1. MEDLINE (1966 to 01 August 2017).
2. Embase (1966 to 01 August 2017).
3. Cochrane Library (01 August 2017; 2017, Issue 8).

We used keywords (to retrieve e-publications and items not indexed in MEDLINE).

1. PubMed (1966 to 01 August 2017).

Others.

1. Conference proceedings of the Perinatal Society of Australia and New Zealand (from 2005 to 01 August 2017).
2. Conference proceedings of the Pediatric Academic Societies (from 2000 to 01 August 2017).

We have presented in Appendix 1 the full search strategies for each database. We screened the reference lists of any cited articles.

Searching other resources

We searched clinical trial registries for ongoing and recently completed trials (e.g. ClinicalTrials.gov (clinicaltrials.gov), World

Health Organization International Trials Registry and Platform, International Standard Randomised Controlled Trial Number (ISRCTN) registry (www.isrctn.com/)).

Data collection and analysis

We used the standard methods of the Cochrane Neonatal Review Group as described below.

Selection of studies

Two review authors (CR and JC) independently searched and identified eligible trials that met the inclusion criteria using Covidence, which is an online screening and data extraction tool used for Cochrane Reviews (Covidence 2017). First, we screened titles and abstracts to identify potentially relevant citations; then we retrieved the full text of all potentially relevant articles. We independently assessed the eligibility of studies in accordance with the specified inclusion criteria. We reviewed studies for relevance based on study design and types of participants, interventions, and outcome measures. We resolved disagreements by discussion and, if necessary, by consultation with a third review author (PD).
We have provided details of studies excluded from the review in the Characteristics of excluded studies table, along with reasons for exclusion. We contacted trial authors if details of primary trials were unclear.

Data extraction and management

Two review authors (CR and JC) separately extracted, assessed, and coded all data for each study using an online screening and data extraction tool for Cochrane Reviews (Covidence 2017). One review author (CR) checked exported data using Review Manager 5 (RevMan 5) software (Review Manager 2014). A third review author addressed disagreements.

Assessment of risk of bias in included studies

Two review authors (CR and JC) independently assessed the risk of bias (as low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool (Higgins 2011) for the following domains.

1. Sequence generation (selection bias).
2. Allocation concealment (selection bias).
3. Blinding of participants and personnel (performance bias).
4. Blinding of outcome assessment (detection bias).
5. Incomplete outcome data (attrition bias).
6. Selective reporting (reporting bias).
7. Any other bias.

We resolved disagreements by discussion or by consultation with a third review author. See Appendix 2 for a detailed description of risk of bias for each domain.

Measures of treatment effect

We performed statistical analyses using standard methods of the Cochrane Neonatal Review Group. We analysed results of studies using RevMan 5 (Review Manager 2014), and we presented results as risk ratios (RRs), risk differences (RDs), number needed to treat for an additional beneficial outcome (NNTB), or number needed to treat for an additional harmful outcome (NNTH) for categorical variables. We used mean differences (MDs) for continuous variables. We reported 95% confidence intervals (95% CIs) for all estimates.

Unit of analysis issues

We included all RCTs and quasi-RCTs. We took into account the level at which randomisation occurred, including cross-over trials, cluster-randomised trials, and multiple observations for the same outcome.

Dealing with missing data

We planned to request additional data from the authors of each trial if data on important outcomes were missing or needed clarification. When data were still missing, we planned to examine the effects of losses by performing sensitivity analysis. We performed these analyses by intention-to-treat.

Assessment of heterogeneity

We assessed statistical heterogeneity by examining the I^2 statistic - a quantity that describes the proportion of variation in point estimates that is due to variability across studies rather than to sampling error (Higgins 2011). We applied I^2 statistic cutoffs and labels for heterogeneity as follows.

1. Less than 25%: no heterogeneity.
2. 25% to 49%: heterogeneity.
3. 50% to 74%: moderate heterogeneity.
4. $\geq$ 75%: high heterogeneity.

We considered statistical heterogeneity to be substantial when the I^2 statistic value was greater than 50%. In addition, we employed the Chi^2 test of homogeneity to determine the strength of evidence that heterogeneity is genuine. We explored clinical variation across studies by comparing the distribution of important participant factors among trials and trial factors (randomisation concealment, blinding of outcome assessment, loss to follow-up, treatment type, and co-interventions). We considered a threshold P value less than 0.1 as an indicator of important heterogeneity (genuine variation in effect sizes).

Assessment of reporting biases

We planned to use funnel plots to assess small-study effects. Owing to several possible explanations for funnel plot asymmetry, we planned to interpret results carefully (Sterne 2011).

Data synthesis

We planned to perform statistical analyses using standard methods of the Cochrane Neonatal Review Group. We used RevMan 5 software with the fixed-effect model for meta-analysis (Review Manager 2014). We used standardised mean differences (SMDs) to combine trials that measured the same outcome using different methods. We used weighted mean differences (WMDs) with 95% CIs for outcomes measured on a continuous scale.

Quality of evidence

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the quality of evidence for the following (clinically relevant) outcomes.

1. Death (as above).
2. Major neurodevelopmental disability (as above).
3. Each component of major neurodevelopmental disability (as above).

Two review authors (CR and JC) independently assessed the quality of evidence for each of the outcomes above. We considered evidence from RCTs as high quality but downgraded the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of evidence, precision of estimates, and presence of publication bias. We used the GRADEpro Guideline Development Tool (GRADEpro GDT) to create Summary of findings for the main comparison to report the quality of evidence.

The GRADE approach yields an assessment of the quality of a body of evidence using one of four grades.

1. High: we are very confident that the true effect lies close to that of the estimate of the effect.
2. Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
3. Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
4. Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate.

Subgroup analysis and investigation of heterogeneity

We carried out the following subgroup analyses.

1. Severity of HIE.
   i) Based on Sarnat score (Finer 1981; Sarnat 1976).
      a) Mild versus moderate/severe.
   ii) Based on EEG or aEEG at baseline.
      a) Mild (electrographic seizures, dysmaturity) versus moderate/severe (low voltage or discontinuous background/isoelectric or burst-suppression pattern).
2. Xenon administration.
   i) Concentration: < 30% versus ≥ 30%.
   ii) Starting age: < six hours versus ≥ six hours after insult.
   iii) Duration: < 12 hours versus ≥ 12 hours.
3. Gestational age.
   i) Late preterm (35 0/7 through 36 6/7 gestational weeks) versus term infants (≥ 37 0/7 gestational weeks).
4. Quality of outcome assessment.
   i) High quality (≥ 18 months with formal psychological testing and review by developmental paediatrician for diagnosis of cerebral palsy (CP)) versus lower quality.

Sensitivity analysis

We conducted sensitivity analyses to explore the effects of methodological quality of trials and to ascertain whether studies at high risk of bias overestimate the effects of treatment.

RESULTS

Description of studies

See Characteristics of included studies and Characteristics of excluded studies tables.

Results of the search

We assessed 89 titles and abstracts in electronic format. We assessed two studies as relevant and determined that one study met the criteria for inclusion (Figure 1, Study flow diagram).

Figure 1. Study flow diagram.

Included studies

Azzopardi 2016

Azzopardi 2016 is a proof-of-concept RCT conducted at four neonatal intensive care units (NICUs) in the UK between January 2012 and September 2014. Researchers randomised 92 infants at gestational age 36 weeks or greater born with evidence of peripartum hypoxia-ischaemia (based upon Apgar score ≤ 5 at 10 minutes after birth, continued need for resuscitation 10 minutes after birth, or acidosis within 1 hour of birth), moderate to severe encephalopathy, and moderately or severely abnormal background activity or seizures as shown by amplitude-integrated EEG. Trialists cooled 46 infants in the intervention group to a target rectal temperature of 33.5°C and provided them with 30% xenon through an uncuffed endotracheal tube connected to a recirculating device developed for the trial. Investigators commenced xenon immediately after randomisation and continued this for 24 hours. Forty-six infants in the control group received standard care and were cooled to a target rectal temperature of 33.5°C with servo-controlled equipment. Researchers started whole-body cooling within six hours of birth and continued this for 72 hours. The primary outcome for the study was a reduction in the lactate-to-N-acetyl aspartate ratio in the thalamus and preserved fractional anisotropy in the posterior limb of the internal capsule, measured by magnetic resonance spectroscopy and magnetic resonance imaging, respectively, within 15 days of birth. Investigators performed prespecified subgroup analyses of the primary outcome by severity of the abnormality on aEEG at randomisation, time from birth to start of xenon therapy, and the relation between these measures and neurological findings at discharge. Secondary outcomes included maximum Thompson HIE score, neurological examination at discharge from the treatment centre, occurrence of seizures, intracranial haemorrhage, persistent hypotension, pulmonary haemorrhage, pulmonary hypertension, prolonged blood coagulation time, thrombocytopaenia, major venous thrombosis, cardiac arrhythmia, culture-proven late-onset sepsis, necrotising enterocolitis, pneumonia, pulmonary air leak, anuria or oliguria, age at which full oral feeding was achieved, duration of hospital stay, and grade of abnormalities on visual analysis of MRI. Study authors recorded serious adverse events and included death, hypertension (mean blood pressure > 85 mmHg), hypotension (mean blood pressure < 25 mmHg), cardiac arrhythmia (severe bradycardia (heart rate < 60 beats per minute) or ventricular arrhythmia), and inability to achieve adequate ventilation despite appropriate adjustment of ventilator settings. They assessed the primary outcome in 41 (89%) of 46 infants in the cooling plus xenon group and in 37 (80%) of 46 infants in the cooling only group. Lactate-to-N-acetyl aspartate ratio in the thalamus and fractional anisotropy values in the posterior limb of the internal capsule were similar in the two groups. The thalamic geometric mean ratio of lactate to N-acetyl aspartate was 1.09 (95% CI 0.90 to 1.32), and the mean difference in fractional anisotropy was -0.01 (95% CI -0.03 to 0.02). Nine (20%) infants in the cooling only group and 11 (24%) infants in the cooling plus xenon group died. Exclusion of deaths from the analysis did not significantly affect results.

Excluded studies

We excluded from this review one potentially relevant study (Azzopardi 2013), which was a nested, non-randomised substudy of a larger RCT (Azzopardi 2016).

Risk of bias in included studies

We judged the included study to be at low risk of bias overall. See the risk of bias graph (Figure 2) and summary (Figure 3).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

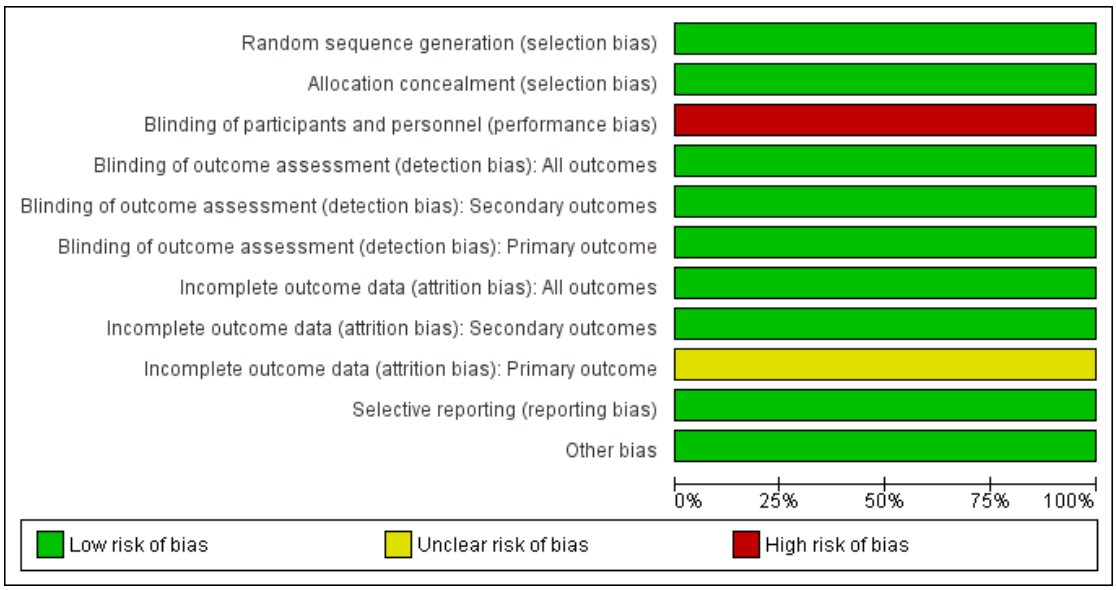


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Allocation

Investigators used a computer-generated randomisation sequence. They concealed allocation to treatment by using a central, web-based system with telephone backup (low risk of bias).

Blinding

This was an open-label trial. Masking of investigators and parents to allocation was not feasible because of the need for a special ventilator to administer xenon (high risk of bias). However, investigators who assessed the primary outcome were masked to treatment allocation (low risk of bias). Unblinded assessors assessed secondary outcomes, but only two of these outcomes were prone to detection bias (Thompson score and neurological assessment at discharge; low risk of bias).

Incomplete outcome data

Investigators presented a complete flow chart for all screened and randomised infants. They randomised a total of 92 infants, 78 (85%) of whom were available for assessment of the primary outcome - 41 (89%) of 46 in the cooling plus xenon group and 37 (80%) of 46 in the cooling alone group. Five (5%) infants did not have MRI scans done, although they were alive at discharge - two (4%) in the cooling plus xenon group and three (7%) in the cooling alone group. Researchers assessed secondary outcomes completely. We judged the risk of attrition bias for all outcomes as low. An additional nine of 92 (9.7%) infants died before discharge and were excluded from the analysis - three of 46 (6.5%) in the cooling plus xenon group and six of 46 (13.0%) in the cooling only group. However, it remains unclear at which postnatal age these deaths occurred (before or after the prespecified 15-day window for MRI). Therefore, we decided to rate the risk of attrition bias for the primary outcome as unclear.

Selective reporting

The study protocol is available, and study authors reported all prespecified primary and secondary outcomes (low risk of bias).

Other potential sources of bias

We identified no other sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison**

Comparison 1: cooling plus xenon versus cooling alone (all infants)

See Summary of findings for the main comparison.

1. Primary outcome.
   i) Death or major neurodevelopmental disability: the included study did not report this outcome.
2. Secondary outcomes.
   i) Mortality (Analysis 1.1, Figure 4).

Figure 4. Forest plot of comparison: 1 Cooling plus xenon versus cooling alone, outcome: 1.1 Mortality.

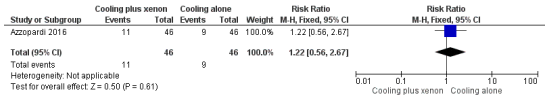
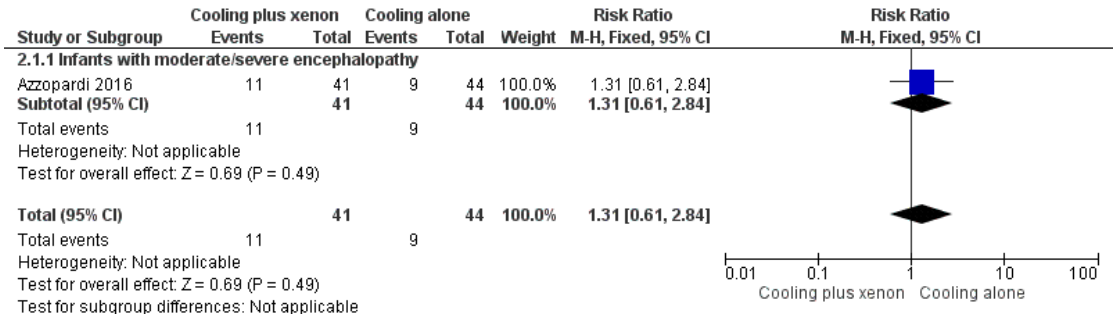


Figure 8. Forest plot of comparison: 2 Cooling plus xenon versus cooling alone: subgroup analysis by baseline severity of encephalopathy, outcome: 2.1 Mortality.



i) Mild encephalopathy (Thompson score 0 to 10): none of the five infants with mild encephalopathy in the cooling plus xenon group and none of the two infants with mild encephalopathy in the cooling alone group died.

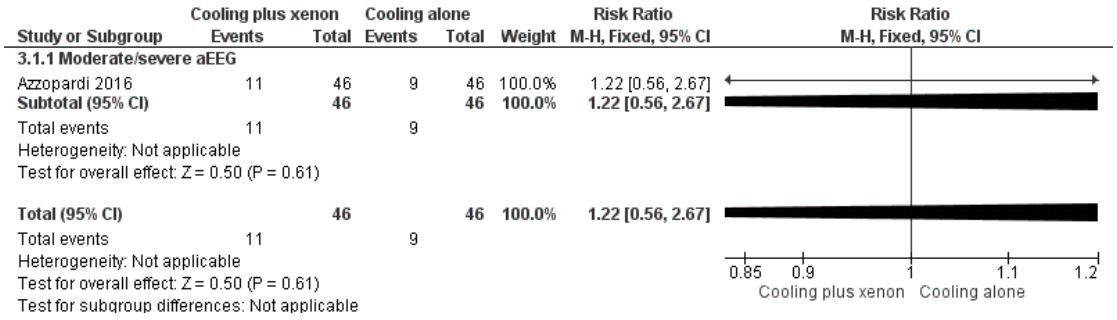
ii) Moderate/severe encephalopathy (Thompson score 11 to 22): nine (20%) of 44 infants with moderate/severe encephalopathy in the cooling plus xenon group and 11 (27%) of 41 infants with moderate/severe encephalopathy in the cooling alone group died. Among infants with moderate/severe encephalopathy, cooling plus xenon was not associated with reduced mortality at the latest reported age (risk ratio (RR) 1.31, 95% CI 0.61 to 2.84; risk difference (RD) 0.06, 95% CI -0.12 to 0.24; one study and 92 infants; low quality evidence).

1. Major neurodevelopmental disability: the included study did not report this outcome.

Comparison 3: cooling plus xenon versus cooling alone: subgroup analysis by baseline amplitude-integrated electroencephalogram (aEEG) findings

1. Death or major neurodevelopmental disability: the included study did not report this outcome.
2. Mortality at latest follow-up (Analysis 3.1, Figure 9).

Figure 9. Forest plot of comparison: 3 Cooling plus xenon versus cooling alone: subgroup analysis by baseline amplitude-integrated electroencephalogram (aEEG) findings, outcome: 3.1 Mortality.



i) Mild aEEG abnormality at baseline: none of the included infants in the cooling plus xenon group and none of the infants in the cooling only group had signs of mild aEEG abnormality at baseline.

ii) Moderate/severe aEEG abnormality at baseline: 11 (24%) of 46 infants with moderate/severe aEEG abnormalities in the cooling plus xenon group and nine (20%) of 46 infants with moderate/severe aEEG abnormalities in the cooling alone group died. Among infants with moderate/severe aEEG abnormalities at baseline, cooling plus xenon was not associated with reduced mortality at the latest reported age (risk ratio (RR) 1.22, 95% CI 0.56 to 2.67; risk difference (RD) 0.04, 95% CI -0.12 to 0.21; one study and 92 infants; low quality evidence).

1. Major neurodevelopmental disability: the included study did not report this outcome

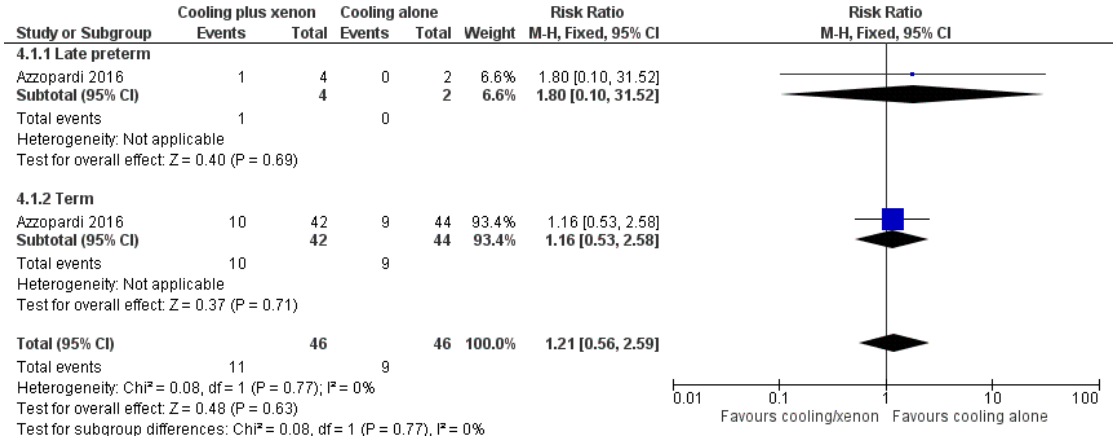
Comparison 4: cooling plus xenon versus cooling alone: subgroup analysis by xenon concentration

1. Death or major neurodevelopmental disability: the included study did not report this outcome.
2. Mortality at the latest follow-up: the included study did not report this outcome.
3. Major neurodevelopmental disability: the included study did not report this outcome.

Comparison 5: cooling plus xenon versus cooling alone: subgroup analysis by gestational age

1. Death or major neurodevelopmental disability: the included study did not report this outcome.
2. Mortality (Analysis 4.1, Figure 10).

Figure 10. Forest plot of comparison: 4 Cooling plus xenon versus cooling alone: subgroup analysis by gestational age, outcome: 4.1 Mortality.



i) Late preterm infants: one (25%) of four late preterm infants in the cooling plus xenon group and none of two late preterm infants in the cooling alone group died. Among late preterm infants with HIE, cooling plus xenon was not associated with reduced mortality at the latest reported age (risk ratio (RR) 1.80, 95% confidence interval (CI) 0.10 to 31.52; risk difference (RD) 0.25, 95% CI -0.33 to 0.83; one study and 92 infants).

ii) Term infants: 10 (24%) of 42 term infants in the cooling plus xenon group and nine (20%) of 44 term infants in the cooling alone group died. Among term infants with HIE, cooling plus xenon was not associated with reduced mortality at the latest reported age (risk ratio (RR) 1.16, 95% CI 0.53 to 2.58; risk difference (RD) 0.03, 95% CI -0.14 to 0.21; one study and 92 infants; low quality evidence).

1. Major neurodevelopmental disability: the included study did not report this outcome.

Comparison 6: cooling plus xenon versus cooling alone: subgroup analysis by quality of follow-up

1. Death or major neurodevelopmental disability: the included study did not report this outcome.
2. Mortality at the latest follow-up: the included study did not report this outcome.
3. Major neurodevelopmental disability: the included study did not report this outcome.

DISCUSSION

Summary of main results

This review identified a single randomised controlled open-label trial looking at the neuroprotective short-term effects of xenon in combination with therapeutic hypothermia after birth asphyxia. The trial randomised 92 newborns with moderate to severe HIE to either cooling plus xenon or cooling alone. The primary outcome - reduction in the lactate-to-N-acetyl aspartate ratio in the thalamus and in preserved fractional anisotropy in the posterior limb of the internal capsule measured with magnetic resonance spectroscopy and magnetic resonance imaging, respectively - was not significantly different between the two groups. Long-term neurodevelopmental outcomes, such as the primary outcome of this review, were not reported. Researchers found no substantial differences between groups for other secondary outcomes, such as mortality and occurrence of seizures during primary hospitalisation. Available data do not show an increased adverse event rate in the cooling plus xenon group compared with the cooling alone group.

Overall completeness and applicability of evidence

The neuroprotective effects of xenon as an adjuvant to cooling have been evaluated only in a single randomised controlled trial. This trial enrolled a small number of participants and did not report long-term neurodevelopmental outcomes. Moreover, infants in the intervention group received a relatively low xenon concentration of 30%, and it may well be that use of higher xenon concentrations (≥ 40%) is effective in reducing brain injury after hypoxic-ischaemic encephalopathy (HIE), as suggested by preclinical studies. Thus, current evidence is inadequate to determine whether xenon therapy for newborns with HIE is safe or effec-

tive. Because of its high costs and complex use of xenon in clinical practice, applicability of evidence is restricted to high-resource settings.

Quality of the evidence

We assessed the quality of evidence for death, major neurodevelopmental disability, and each component of major neurodevelopmental disability (Summary of findings for the main comparison). We were able to include only one randomised controlled trial (RCT) in this review; therefore we were not able to assess the level of evidence for inconsistency. However, the included trial reported short-term outcomes for the control group (cooling alone) similar to those seen in the cooled groups of prior cooling trials (Azzopardi 2014; Gluckman 2005; Shankaran 2005). Owing to the small sample included and the research question addressed, we downgraded the level of evidence for imprecision and indirectness. Although the included trial was at low risk of bias, we judged the overall quality of evidence as low.

Potential biases in the review process

We are aware of no bias in our review process.

Agreements and disagreements with other studies or reviews

We are aware of no other systematic reviews on this topic.

AUTHORS' CONCLUSIONS

Implications for practice

Currently available evidence does not support the routine use of xenon as a neuroprotective agent for newborns with HIE and suggests that this practice should be limited to RCTs.

Implications for research

The biological plausibility of using xenon to prevent HIE injury has been well established in preclinical studies (Dingley 2006; Ma 2005), and available clinical data have not raised major safety concerns related to use of xenon in newborn infants (Azzopardi 2016). Further large trials may be justified and should focus on effects of various xenon concentrations and timing regimens on long-term neurodevelopmental outcomes.

ACKNOWLEDGEMENTS

None.

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Sun L. Early childhood general anaesthesia exposure and neurocognitive development. *British Journal of Anaesthesia* 2010;**105**(Suppl 1):i61–8. DOI: 10.1093/bja/aeq302; PUBMED: 21148656

Thayyil 2010

Thayyil S, Chandrasekaran M, Taylor A, Bainbridge A, Cady EB, Chong WK, et al. Cerebral magnetic resonance biomarkers in neonatal encephalopathy: a meta-analysis. *Pediatrics* 2010;**125**(2):e382–95. DOI: 10.1542/peds.2009-1046; PUBMED: 20083516

Thoresen 2009

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Azzopardi 2016

Methods	Proof-of-concept, randomised, open-label, parallel-group trial done at 4 neonatal intensive care units in the United Kingdom
Participants	**Included infants** born between 36 and 43 weeks' gestational age with signs of moderate to severe encephalopathy and moderately or severely abnormal background activity for at least 30 minutes, or seizures as shown by amplitude-integrated EEG, with 1 of the following: Apgar score ≤ 5 at 10 minutes after birth, continued need for resuscitation 10 minutes after birth, or acidosis within 1 hour of birth **Excluded infants** were older than 6 hours when cooling was started or were older than12 hours at randomisation. Infants were excluded if their oxygen requirement was greater than 60%, if they needed nitric oxide inhalation or ventilation with a high-frequency oscillator, if they needed extracorporeal membrane oxygenation, or if they had major congenital abnormalities **Total number of participants:** N = 92 **Baseline characteristics:** - Mean (SD) gestational age at delivery (weeks): cooling plus xenon = 39.8 (1.3), cooling alone = 39.8 (1.3) - Mean (SD) birthweight (g): cooling plus xenon 3392 (685), cooling alone = 3213 (448) - Male sex (n): cooling plus xenon = 26 (57%), cooling alone = 21 (46%) - Median (IQR) Apgar at 10 minutes: cooling plus xenon = 5 (3 to 6), cooling alone = 5 (4 to 7) - Median (IQR) cord or first blood pH: cooling plus xenon = 6.9 (6.8 to 7.1), cooling alone = 6.9 (6.7 to 7.0) - Median (IQR) age cooling commenced (hours): cooling plus xenon = 0.2 (0.0 to 1.5) , cooling only = 0.3 (0.0 to 0.8) - Mild HIE at trial entry (n): cooling plus xenon = 5 (11%), cooling alone = 2 (4%) - Moderate HIE at trial entry (n): cooling plus xenon = 21 (46%), cooling alone = 30 (65%) - Severe HIE at trial entry (n): cooling plus xenon = 20 (43%), cooling alone = 14 (30%) - Moderate EEG/aEEG abnormality at trial entry (n): cooling plus xenon = 6 (13%), cooling alone = 7 (15%) - Severe EEG/aEEG abnormality at trial entry (n): cooling plus xenon = 40 (87%), cooling alone = 39 (85%)
Interventions	**Standard care (n = 46):** whole body cooling to a target rectal temperature of 33.5°C for 72 hours starting within 6 hours of birth. If cooling equipment was not available at the referring hospital, passive cooling was commenced and active cooling was started by the transport team and continued during transport to the treatment centre **Intervention (n = 46):** cooled infants in the inhaled xenon group received 30% xenon through an uncuffed endotracheal tube connected to a recirculating device developed for this trial. Xenon was commenced immediately after randomisation and continued for 24 hours **Intervention characteristics:** - Mean (SD) xenon concentration (%): 32.2 (6.9)

	- Median (IQR) starting age of xenon administration (hours): 10 (8.2 to 11.2) - Median (IQR) duration of xenon administration (hours): 24 (24 to 24)
Outcomes	**Primary:** reduction in the lactate-to-N-acetyl aspartate ratio in the thalamus on MRS or preserved FA in the posterior limb of the internal capsule, measured by magnetic resonance spectroscopy and MRI, respectively, within 15 days of birth **Secondary:** maximum Thompson HIE score, neurological examination at discharge from treatment centre, occurrence of seizures, intracranial haemorrhage, persistent hypotension, pulmonary haemorrhage, pulmonary hypertension, prolonged blood coagulation time, thrombocytopaenia, major venous thrombosis, cardiac arrhythmia, culture-proven late-onset sepsis, necrotising enterocolitis, pneumonia, pulmonary air leak, anuria or oliguria, age at which full oral feeding was achieved, duration of hospital stay, grade of abnormalities on visual analysis of MRI
Identification	ClinicalTrials.gov: NCT00934700 ISRCTN: ISRCTN08886155
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate, with a computer-generated randomisation sequence. Assignment done through a secure web-based system with telephone backup
Allocation concealment (selection bias)	Low risk	Adequate, central allocation system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study was unblinded with regards to intervention allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Detection bias judged as low risk for primary outcome and as low risk for secondary outcomes (see below)
Blinding of outcome assessment (detection bias) Secondary outcomes	Low risk	Assessors of outcomes unblinded to treatment allocation; however, only 2 secondary outcomes reliant on assessors (Thompson score and neurological assessment at discharge). The other outcomes are less likely to be prone to bias
Blinding of outcome assessment (detection bias) Primary outcome	Low risk	Investigators who assessed the primary outcome were masked to treatment allocation

Azzopardi 2016 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete flow chart of all screened and randomised infants available. Fourteen (15.2%) infants were excluded after randomisation, nine (9.7%) of whom died before discharge
Incomplete outcome data (attrition bias) Secondary outcomes	Low risk	Complete assessment of secondary outcomes (92/92)
Incomplete outcome data (attrition bias) Primary outcome	Unclear risk	The primary outcome was assessed in 41 (89%) of 46 infants in the cooling plus xenon group and in 37 (80%) of 46 infants in the cooling only group. In 2/46 (4.3%) infants in the cooling plus xenon group and in 3/46 (6.5%) infants in the cooling alone group, MRI scans were not done, although infants were alive at discharge. An additional 9/92 (9.7%) patients died before discharge and were excluded from the analysis - 3/46 (6.5%) in the cooling plus xenon group and 6/46 (13.0%) in the cooling only group. However, it remains unclear at which postnatal age these deaths occurred (before or after the prespecified 15-day window for the MRI). Therefore, we decided to rate the risk of attrition bias as "unclear"
Selective reporting (reporting bias)	Low risk	Study protocol available online; all prespecified primary and secondary outcomes reported
Other bias	Low risk	None apparent

aEEG: amplitude-integrated electroencephalogram.
EEG: electroencephalogram.
FA: fluorescent antibody.
HIE: hypoxic-ischaemic encephalopathy.
IQR: interquartile ratio.
MRI: magnetic resonance imaging.
MRS: magnetic resonance spectroscopy.
SD: standard deviation.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Azzopardi 2013	Nested, non-randomised substudy of larger randomised controlled trial (Azzopardi 2016)

Characteristics of ongoing studies *[ordered by study ID]*

NCT01545271

Trial name or title	Xenon and Cooling Therapy in Babies at High Risk of Brain Injury Following Poor Condition at Birth: Randomised Pilot Study (The CoolXenon2 Study)
Methods	Randomised controlled single-centre pilot study in UK
Participants	**Includes:** infants born at ≥ 36 weeks' gestation WITH clinical evidence of peripartum hypoxia-ischaemia (Apgar score ≤ 5 at 10 minutes, continued need for resuscitation at 10 minutes, or severe acidosis (pH < 7 or base deficit ≥ 16 mmol/L in cord blood or arterial/venous blood within 60 minutes of birth)) AND abnormal amplitude-integrated electroencephalogram background AND moderate or severe encephalopathy (Sarnat criteria) with 1 of hypotonia, abnormal reflexes, absent or weak suck, clinical seizures, or a combination. For xenon therapy, infants must be intubated with normal partial pressure of CO_2 (pCO_2), positive end-expiratory pressure < 6 cm H_2O and fraction of inspired oxygen (FiO_2) < 0.40, seizures under control, weighing > 2.3 kg and < 5 hours old, with birthweight greater than the second percentile for age, with no major congenital anomalies, and haemodynamically stable with no evidence of infection **Excludes:** infants considered futile and infants not meeting above criteria
Interventions	**Standard care:** cooling to 33.5°C body temperature, starting within 3 hours after birth **Intervention:** cooling to 33.5°C body temperature plus xenon gas at 50% concentration for 18 hours, started within 5 hours after birth
Outcomes	**Primary outcomes:** amplitude-integrated electroencephalogram (aEEG) grading: number of hours after birth when aEEG voltage has reached normal or discontinuous normal pattern. Brain MRI findings before 2 weeks of age **Secondary outcomes:** not provided
Starting date	May 2012
Contact information	Marianne Thoresen, MD
Notes	NCT01545271

NCT02071394

Trial name or title	Xenon and Cooling Therapy in Babies at High Risk of Brain Injury Following Poor Condition at Birth: A Randomised Pilot Outcomes Study (CoolXenon3 Study)
Methods	Randomised controlled pilot outcomes study at 2 centres in the UK
Participants	**Includes:** infants born at ≥ 36 weeks' gestation WITH clinical evidence of peripartum hypoxia-ischaemia (Apgar score ≤ 5 at 10 minutes, continued need for resuscitation at 10 minutes, or severe acidosis (pH < 7 or base deficit ≥ 16 mmol/L in cord blood or arterial/venous blood within 60 minutes of birth)) AND abnormal amplitude-integrated electroencephalogram background AND moderate or severe encephalopathy (Sarnat criteria) with 1 of hypotonia, abnormal reflexes, absent or weak suck, clinical seizures, or a combination For xenon therapy, infants must be intubated with normal partial pressure of CO_2 (pCO_2), positive end-expiratory pressure < 8 cm H_2O and fraction of inspired oxygen (FiO_2) < 0.40, seizures under control, < 5 hours old, with birthweight greater than the second percentile for age, with no major congenital anomalies, and haemodynamically stable **Excludes:** infants older than 3 hours of age when cooling started, infants considered futile, and infants not meeting above criteria
Interventions	**Standard care:** cooling to 33.5°C body temperature, starting within 3 hours after birth **Intervention:** cooling to 33.5°C body temperature plus xenon gas at 50% concentration for 18 hours, started within 5 hours after birth
Outcomes	**Primary outcomes:** death and moderate or severe disability (Bayley III) at 18 months of age **Secondary outcomes:** brain MRI within 2 weeks of birth and before hospital discharge, amplitude-integrated electroencephalogram (aEEG) grading within 1 week of birth, number of hours after birth when aEEG voltage has reached a normal or discontinuous normal pattern, Dubovitz score within 7 days, number of normal infants (Bayley III composite score ≥ 85 and no neurosensory disability) at 18 to 24 months of age
Starting date	March 2014
Contact information	Marianne Thoresen, MD
Notes	NCT02071394

aEEG: amplitude-integrated electroencephalogram.
CO_2: carbon dioxide.
FiO_2: fraction of inspired oxygen.
MRI: magnetic resonance imaging.
pCO_2: partial pressure of CO_2.

DATA AND ANALYSES

Comparison 1. Cooling plus xenon versus cooling alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	1	92	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.56, 2.67]
2 Adverse event: cardiac arrhythmia	1	92	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.10, 2.60]
3 Adverse event: persistent hypotension	1	92	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.79, 1.44]
4 Adverse event: respiratory impairment	1	92	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.45, 2.89]

Comparison 2. Cooling plus xenon versus cooling alone: subgroup analysis by baseline severity of encephalopathy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	1	85	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.61, 2.84]
1.1 Infants with moderate/ severe encephalopathy	1	85	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.61, 2.84]

Comparison 3. Cooling plus xenon versus cooling alone: subgroup analysis by baseline amplitude-integrated electroencephalogram (aEEG) findings

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	1	92	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.56, 2.67]
1.1 Moderate/severe aEEG	1	92	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.56, 2.67]

Comparison 4. Cooling plus xenon versus cooling alone: subgroup analysis by gestational age

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	1	92	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.56, 2.59]
1.1 Late preterm	1	6	Risk Ratio (M-H, Fixed, 95% CI)	1.8 [0.10, 31.52]
1.2 Term	1	86	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.53, 2.58]

Analysis 1.1. Comparison 1 Cooling plus xenon versus cooling alone, Outcome 1 Mortality.

Review: Xenon as an adjuvant to therapeutic hypothermia in near-term and term newborns with hypoxic-ischaemic encephalopathy

Comparison: 1 Cooling plus xenon versus cooling alone

Outcome: 1 Mortality

Study or subgroup	Cooling plus xenon n/N	Cooling alone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Azzopardi 2016	11/46	9/46		100.0 %	1.22 [0.56, 2.67]
Total (95% CI)	**46**	**46**		**100.0 %**	**1.22 [0.56, 2.67]**

Total events: 11 (Cooling plus xenon), 9 (Cooling alone)
Heterogeneity: not applicable
Test for overall effect: Z = 0.50 (P = 0.61)
Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Cooling plus xenon versus cooling alone, Outcome 2 Adverse event: cardiac arrhythmia.

Review: Xenon as an adjuvant to therapeutic hypothermia in near-term and term newborns with hypoxic-ischaemic encephalopathy

Comparison: 1 Cooling plus xenon versus cooling alone

Outcome: 2 Adverse event: cardiac arrhythmia

Study or subgroup	Cooling plus xenon n/N	Cooling alone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Azzopardi 2016	2/46	4/46		100.0 %	0.50 [0.10, 2.60]
Total (95% CI)	**46**	**46**		**100.0 %**	**0.50 [0.10, 2.60]**
Total events: 2 (Cooling plus xenon), 4 (Cooling alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.82 (P = 0.41)					
Test for subgroup differences: Not applicable					

Analysis 1.3. Comparison 1 Cooling plus xenon versus cooling alone, Outcome 3 Adverse event: persistent hypotension.

Review: Xenon as an adjuvant to therapeutic hypothermia in near-term and term newborns with hypoxic-ischaemic encephalopathy

Comparison: 1 Cooling plus xenon versus cooling alone

Outcome: 3 Adverse event: persistent hypotension

Study or subgroup	Cooling plus xenon n/N	Cooling alone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Azzopardi 2016	31/46	29/46		100.0 %	1.07 [0.79, 1.44]
Total (95% CI)	**46**	**46**		**100.0 %**	**1.07 [0.79, 1.44]**
Total events: 31 (Cooling plus xenon), 29 (Cooling alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.44 (P = 0.66)					
Test for subgroup differences: Not applicable					

Analysis 1.4. Comparison 1 Cooling plus xenon versus cooling alone, Outcome 4 Adverse event: respiratory impairment.

Review: Xenon as an adjuvant to therapeutic hypothermia in near-term and term newborns with hypoxic-ischaemic encephalopathy

Comparison: 1 Cooling plus xenon versus cooling alone

Outcome: 4 Adverse event: respiratory impairment

Study or subgroup	Cooling plus xenon n/N	Cooling alone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Azzopardi 2016	8/46	7/46		100.0 %	1.14 [0.45, 2.89]
Total (95% CI)	**46**	**46**		**100.0 %**	**1.14 [0.45, 2.89]**
Total events: 8 (Cooling plus xenon), 7 (Cooling alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.28 (P = 0.78)					
Test for subgroup differences: Not applicable					

Analysis 2.1. Comparison 2 Cooling plus xenon versus cooling alone: subgroup analysis by baseline severity of encephalopathy, Outcome 1 Mortality.

Review: Xenon as an adjuvant to therapeutic hypothermia in near-term and term newborns with hypoxic-ischaemic encephalopathy

Comparison: 2 Cooling plus xenon versus cooling alone: subgroup analysis by baseline severity of encephalopathy

Outcome: 1 Mortality

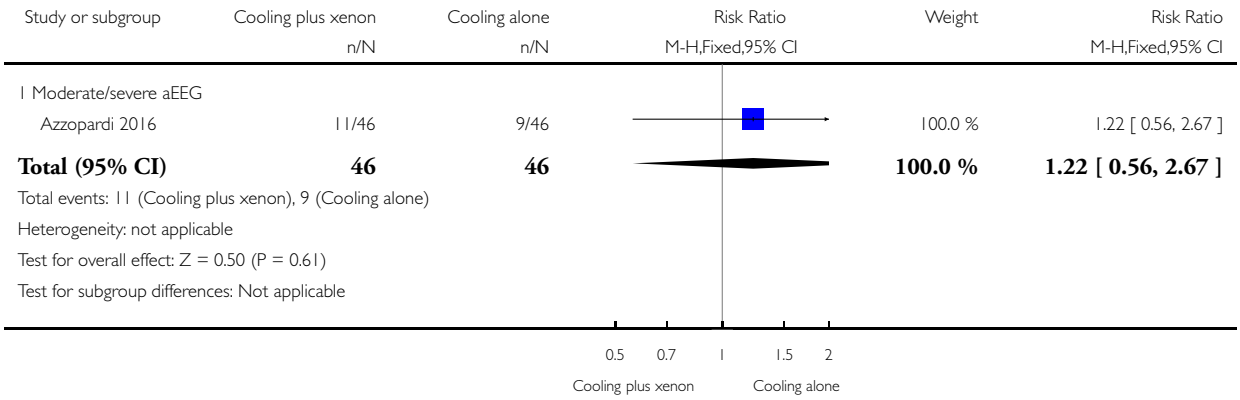
Study or subgroup	Cooling plus xenon n/N	Cooling alone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Infants with moderate/severe encephalopathy					
Azzopardi 2016	11/41	9/44		100.0 %	1.31 [0.61, 2.84]
Total (95% CI)	**41**	**44**		**100.0 %**	**1.31 [0.61, 2.84]**
Total events: 11 (Cooling plus xenon), 9 (Cooling alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.69 (P = 0.49)					
Test for subgroup differences: Not applicable					

Analysis 3.1. Comparison 3 Cooling plus xenon versus cooling alone: subgroup analysis by baseline amplitude-integrated electroencephalogram (aEEG) findings, Outcome 1 Mortality.

Review: Xenon as an adjuvant to therapeutic hypothermia in near-term and term newborns with hypoxic-ischaemic encephalopathy

Comparison: 3 Cooling plus xenon versus cooling alone: subgroup analysis by baseline amplitude-integrated electroencephalogram (aEEG) findings

Outcome: 1 Mortality

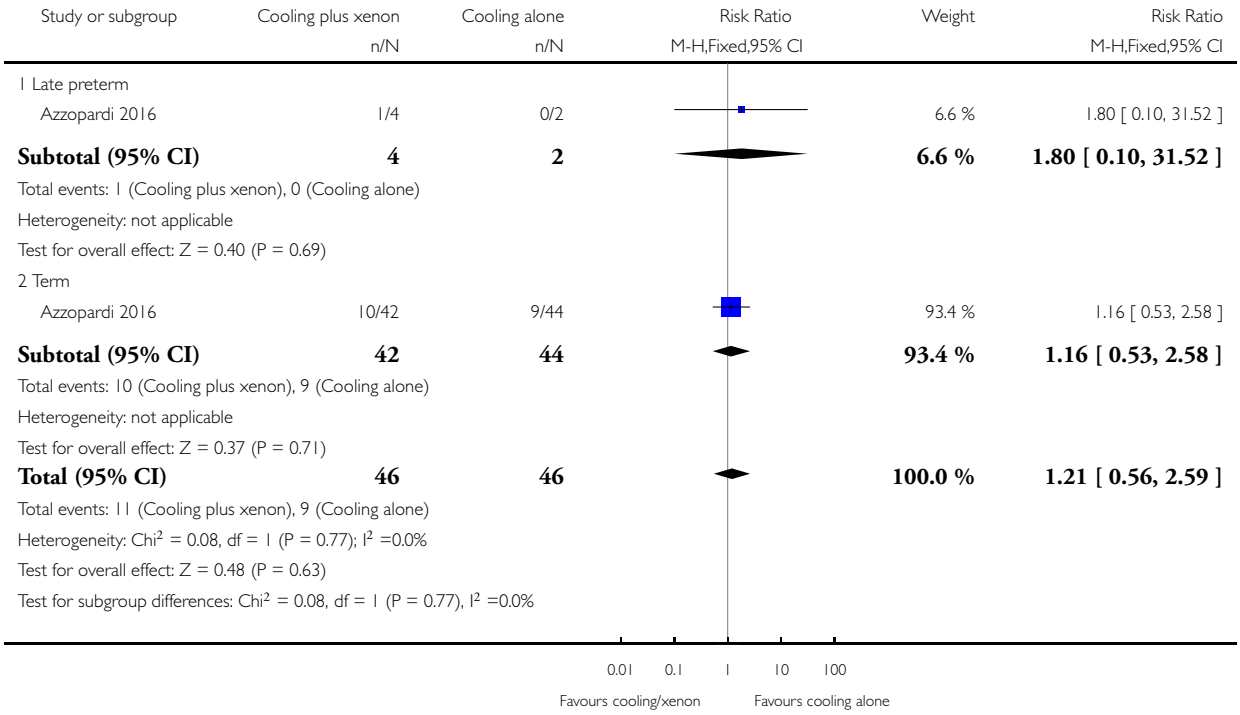


Analysis 4.1. Comparison 4 Cooling plus xenon versus cooling alone: subgroup analysis by gestational age, Outcome 1 Mortality.

Review: Xenon as an adjuvant to therapeutic hypothermia in near-term and term newborns with hypoxic-ischaemic encephalopathy

Comparison: 4 Cooling plus xenon versus cooling alone: subgroup analysis by gestational age

Outcome: 1 Mortality



APPENDICES

Appendix 1. Search strategy

MEDLINE (Ovid)

1. Asphyxia neonatorum/
2. Hyoxia-Ischemia, Brain/
3. exp Anoxia/
4. exp Hypothermia, Induced/ OR hypothermia/
5. Xenon/

6. (birth or newborn* or neonat* or infan* or gestation* or near-term or term or perinatal or prematur* or pre-term or preterm or low-birth-weight or LBW or VLBW or ("35" adj5 week*) or ("36" adj5 week*) or ("37" adj5 week*) or ("38" adj5 week*) or ("39" adj5 week*) or ("40" adj5 week*) or ("41" adj5 week*) or ("42" adj5 week*) or ("43" adj5 week*) or ("44" adj5 week*)).af.
7. (2 or 3) and 4 and 5 and 6
8. 1 and 4 and 5
9. 7 or 8
10. exp animals/ not human*.sh
11. 9 not 10

Embase (Ovid)

1. (birth or newborn* or neonat* or infan* or gestation* or near-term or term or perinatal or prematur* or pre-term or preterm or low-birth-weight or LBW or VLBW or ("35" adj5 week*) or ("36" adj5 week*) or ("37" adj5 week*) or ("38" adj5 week*) or ("39" adj5 week*) or ("40" adj5 week*) or ("41" adj5 week*) or ("42" adj5 week*) or ("43" adj5 week*) or ("44" adj5 week*)).af.
2. hypoxic ischaemic encephalopathy/
3. exp asphyxia/
4. brain hypoxia
5. (neonatal adj asphyxial adj seizure*).tw,kw,hw.
6. xenon/
7. hypothermia/
8. induced hypothermia
9. (2 or 3 or 4) and 6 and (7 or 8) and 1
10. 5 and 6 and (7 or 8)
11. 9 or 10
12. exp ANIMAL/ not human*.sh.
13. 11 not 12

Cochrane Library (Wiley)

1. MeSH descriptor: [Asphyxia Neonatorum] this term only
2. Asphyxia* or Hypoxia or Hypoxic or Hypoxemia or Hypoxaemia or Ischemia or Ischaemia or Ischemic or Ischaemic or anoxia or anoxic (Word variations have been searched)
3. MeSH descriptor: [Hypoxia-Ischemia, Brain] this term only
4. MeSH descriptor: [Anoxia] explode all trees
5. MeSH descriptor: [Hypothermia, Induced] explode all trees
6. MeSH descriptor: [Hypothermia] this term only
7. Hypothermia or Cooling (Word variations have been searched)
8. MeSH descriptor: [Xenon] this term only
9. Xenon or Xe (Word variations have been searched)
10. (35 or 36 or 37 or 38 or 39 or 40 or 41 or 42) next week* (Word variations have been searched)
11. birth or newborn* or neonat* or infan* or gestation* or near-term or "near term" or term or perinatal or prematur* or pre-term or preterm or "pre term" or "low birth weight" or "low birth-weight" or LBW or VLBW (Word variations have been searched)
12. MeSH descriptor: [Infant] explode all trees
13. (2 or 3 or 4) and (5 or 6 or 7) and (8 or 9) and (10 or 11 or 12)
14. (1) and (5 or 6 or 7) and (8 or 9)
15. 13 or 14

PubMed

1. (birth OR newborn* OR neonat* OR infan* OR gestation* OR near-term OR term OR perinatal OR prematur* OR pre-term OR preterm OR "pre term" OR "low birth weight" OR "low birth-weight" OR LBW OR VLBW OR ((35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42) AND weeks)) AND (Asphyxia* OR Hypoxia OR Hypoxic OR Hypoxemia OR Hypoxaemia OR

Ischemia OR Ischaemia OR Ischemic OR Ischaemic) AND (Hypothermia OR Cooling) AND (Xenon OR Xe) AND (NOTNLM OR publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb] OR indatareview[sb] OR pubstatusaheadofprint)

Appendix 2.
' Risk of bias' tool

We will evaluate the following issues and will enter findings into the ' Risk of bias' table.

1. Sequence generation (checking for possible selection bias)

Was the allocation sequence adequately generated?

For each included study, we will categorise the method used to generate the allocation sequence as follows.

1. Low risk (any truly random process, e.g. random number table; computer random number generator).
2. High risk (any non-random process, e.g. odd or even date of birth; hospital or clinic record number).
3. Unclear risk.

2. Allocation concealment (checking for possible selection bias)

Was allocation adequately concealed?

For each included study, we will categorise the method used to conceal the allocation sequence as follows.

1. Low risk (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes).
2. High risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth).
3. Unclear risk.

3. Blinding of participants and personnel (checking for possible performance bias)

Was knowledge of the allocated intervention adequately prevented during the study?

For each included study, we will categorise the methods used to blind study participants and personnel from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes. We will categorise the methods according to the following.

1. Low risk, high risk, or unclear risk for participants.
2. Low risk, high risk, or unclear risk for personnel.

4. Blinding of outcome assessment (checking for possible detection bias)

Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?

For each included study, we will categorise the methods used to blind outcome assessment. We will assess blinding separately for different outcomes or classes of outcomes. We will categorise the methods as follows.

1. Low risk for outcome assessors.
2. High risk for outcome assessors.
3. Unclear risk for outcome assessors.

5. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

Were incomplete outcome data adequately addressed?

For each included study and for each outcome, we will describe the completeness of data including attrition and exclusions from the analysis. We will note whether attrition and exclusions were reported, numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion when reported, and whether missing data were balanced across groups or were related to outcomes. When sufficient information is reported or supplied by the trial authors, we will re-include missing data in the analyses. We will categorise methods as one of the following.

1. Low risk (< 20% missing data).
2. High risk (≥ 20% missing data).
3. Unclear risk.

6. Selective reporting bias

Are reports of the study free of the suggestion of selective outcome reporting?

For each included study, we will describe how we investigated the possibility of selective outcome reporting bias and what we found. We will assess methods as one of the following.

1. Low risk (when it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported).
2. High risk (when not all of the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified outcomes of interest and are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported).
3. Unclear risk.

7. Other sources of bias

Was the study apparently free of other problems that could put it at high risk of bias?

For each included study, we will describe any important concerns we had about other possible sources of bias (e.g. whether a potential source of bias was related to the specific study design, whether the trial was stopped early owing to some data-dependent process). We will assess whether each study was free of other problems that could put it at risk of bias as follows.

1. Low risk.
2. High risk.
3. Unclear risk.

If needed, we plan to explore the impact of the level of bias through undertaking sensitivity analyses.

CONTRIBUTIONS OF AUTHORS

- Christoph Rüegger: responsible for all aspects of review - search; data abstraction, entry, and analysis; manuscript; and editing of review.
- Peter Davis: manuscript preparation; critical review of manuscript.
- Jeanie Cheong: data abstraction and entry; manuscript preparation; critical review of manuscript.

DECLARATIONS OF INTEREST

- Christoph Rüegger: nothing to declare.
- Peter Davis: nothing to declare.
- Jeanie Cheong: nothing to declare.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.